

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
HSIAO, et al.

Application No.: 10/516,864
Filed: 03/30/2006

Conformation No.: 8549

Title: PLASMA OR SERUM MARKER AND
PROCESS FOR DETECTION OF CANCER

Examiner: GOLDBERG, JEANINE

Art Unit: 1634

Docket No: H1584-26-US

Customer No.: 40614

Submitted via EFS-WEB

BRIEF ON APPEAL

This is an appeal from the Final Office Action mailed August 14, 2009 in the above-referenced case. A notice of appeal was filed November 10, 2009 and Appellant hereby petitions to extend the time to file this Appeal Brief by one month.

REAL PARTY IN INTEREST

The Hong Kong University of Science and Technology
Clear Water Bay, Kowloon
Hong Kong, SAR
P.R. China

RELATED APPEALS AND INTERFERENCES

None

STATUS OF CLAIMS

Claims 1- 5 and 30-37 are pending in the present application and claims 6-29 have been canceled.

Claims 1-5, 30-37 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

STATUS OF AMENDMENTS

No amendment was filed subsequent to final rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to a sensitive method for detecting colorectal cancer, particularly at an early stage. The method is based on the measurement of the blood level of beta-catenin associated RNA, DNA, or both, because it is demonstrated that these beta-catenin associated nucleic acids can be clearly detected in all the patients tested while they are not detectable (or detected at a significantly lower level) using the measurement methods under the particular conditions disclosed in the specification. This method is simple with a high degree of accuracy, requiring small volumes of blood sample, which can be obtained by non-invasive, normal blood-drawing procedures.(see paragraphs [0008-0009] of the published application).

The validity and operability of the present invention was confirmed by a subsequently published embodiment in the Wong paper (Wong et al, Clinical Cancer Research, Vol. 10, 1613-1617, March 1, 2004).

GROUNDS OF REJECTION TO BE REVIEWED

(1) Rejection of claims 1-5, 30-37 under 35 U.S.C. § 112, first paragraph, based on the following reference:

1. Wong et al, (*Clinical Cancer Research*, Vol. 10, 1613-1617, March 1, 2004)
2. Osman et al (*Clin Cancer Res.* Vol. 12, No. 11, June 2006)
3. Fleischhacker et al. (*Biochimica et Biophysica Acta*, Vol. 1775, 2007).

GROUP OF CLAIMS

Claims 1-5, 30-37 are commonly rejected in a single group. With respect to the ground of rejection subject to this appeal, the claims will not stand and fall together unless a claim selected as representative of the group for review shares with all other claims in the group a common limitation that is deemed as being non-enabling, see *Hyatt v. Dudas*, 89 USPQ2D 1465, 1469 ((Fed. Cir. 2008) .

ARGUMENTS

I. PRIMA FACIE CASE OF NON-ENABLEMENT HAS EVER BEEN MADE

Through the lengthy prosecution and repeated office actions, the Examiner has never made a *prima facie* case of non-enablement under 35 U.S.C. §112, first paragraph. Take claim 3 as a representative of the rejected claims, which was reproduced below for easy reference, the Examiner has never specifically alleged, let alone articulated, that any of the steps recited in the claim could not have been performed by a person of ordinary skill in the art.

Claim 3 (after incorporating limitations recited in claim 1 on which claim 3 depends):

A method for detecting colorectal carcinoma in a patient, comprising:
extracting blood serum or plasma from the patient;
measuring an amount of beta-catenin RNA in the blood serum or plasma; and
determining a possibility of the presence of colorectal cancer in the patient
based on the amount of beta-catenin RNA measured in the blood serum or
plasma.

The Examiner has never specifically alleged that a person of ordinary skill in the art could not be enabled to extract blood serum or plasma from the patient.

The Examiner has never specifically alleged that a person of ordinary skill in the art could not be enabled to measure the amount of beta-catenin RNA in the blood serum or plasma.

The Examiner has never specifically alleged that a person of ordinary skill in the art could not be enabled to determine a possibility of the presence of colorectal cancer in the patient based on the amount of beta-catenin RNA in the blood serum or plasma as measured according to the specific teaching of the present invention.

All the Examiner did in the repeated office actions was making the same boilerplate statements made under the headings (a) The Nature of the Invention and Breadth of Claims; (b) The Unpredictability of the Art and the State of the Prior Art; (c) Guidance in the Specification; and (d) Quantity of Experimentation. These statements are general and conclusive and never made in connection with the particular issue in the instant application – why a person of ordinary skill in the art cannot perform the step of:

- (1) **Extracting** blood serum or plasma from the patient,
- (2) **Measuring** the amount of beta-catenin RNA in the blood serum or plasma, and
- (3) **Determining** a possibility of the presence of colorectal cancer in the patient based on the amount of beta-catenin RNA measured in the blood serum or plasma according to the teaching of this specification, where the correlation between colorectal cancer and beta-catenin RNA level is clearly shown in the present specification as follows:

Subjects	beta-catenin mRNA (range) (copy)	beta-catenin mRNA (median) (copy)
Carcinoma	6,700-44,000	22,000
Adenoma	690-1800	1,100
Normal	0-169	36

Appellant respectfully submits that it is indisputable that the above results of a specific embodiment described in the specification themselves are *prima facie* enabling to a person of ordinary skill in the art to practice the claimed invention:

determining a possibility of the presence of colorectal cancer in the patient based on the amount of beta-catenin nucleic acid measured in the blood serum or plasma.

Rather than identifying and focusing on the real specific issue why a person of ordinary skill is not enabled to perform any specific step of the claims, the Examiner makes empty assertions under the boilerplate categories. These assertions and the way of using the references as support indicate the lack of basic understanding of the art to examine this application. For example, to people with a basic understanding of the art, the Wong reference, as detailed below, is clearly the evidence supporting the validity of the claimed invention.

II. RELIANCE ON UNSTATED AND UNSUPPORTED PREMISE IS ERRONEOUS AS A MATTER OF LAW

As discussed in the foregoing, the Examiner made no attempt to allege any of the specified elements recited in the rejected claims is non-enabling. Rather, the rejection is implicitly based on an unstated premise: the experimental results about the correlation disclosed in the specification are not believable or trustworthy. Only if this premise were valid, could the non-enabling rejection in the present case be reasonably supported. However, this premise is not explicitly stated, let alone being articulated and supported with reason and/or evidence.

It is respectfully submitted that patent rejection cannot be premised on the Examiner's imagination. Such practice is improper as a matter of law. The Court of Appeals for the Federal Circuit stated that "[t]he PTO cannot make this type of rejection, however, unless it has reason to doubt the objective truth of the statements contained in the written description. See *In Re Cortright*, 49 USPQ2D 1464,1466 (CAFC, 1999) . The court further cites its predecessor court's statement :

“ [A]specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be

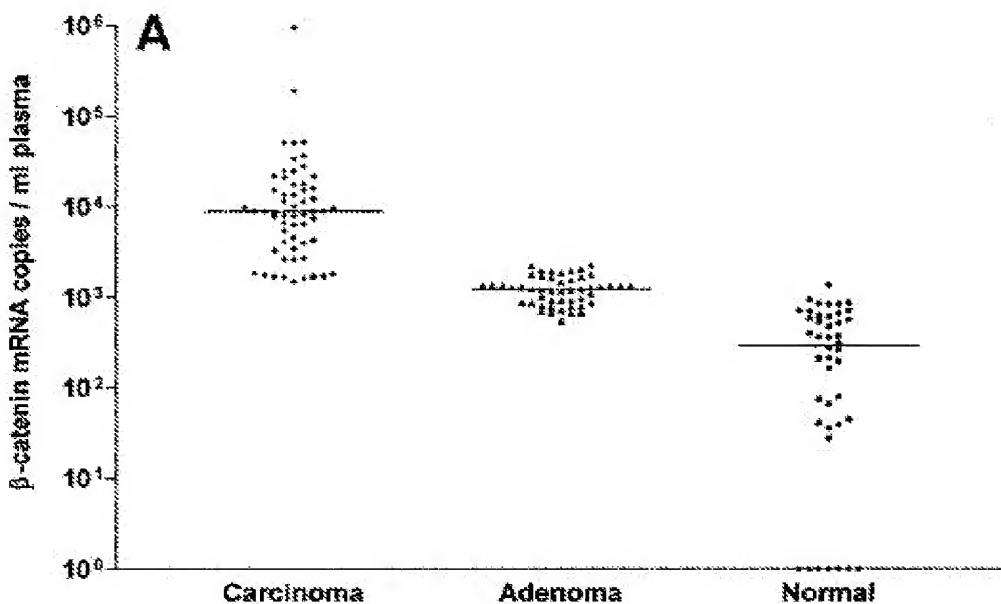
patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.”

In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971) (*emphasis added*). According to the court, in cases where, as it is here, the invention description itself is enabling on its face, the claims cannot be rejected for lack of enablement unless there is reason to suggest that the description by the inventor is untrustworthy or unbelievable. In this case, while implicitly relying on this premise, the Examiner never articulates any reason why he or she cannot believe that the working examples described in the specification cannot work as described. Therefore, the rejection of non-enabling based on an unstated and unsupported premise must be set aside as a matter of law.

III. RELIANCE ON THREE CITED REFERENCES IS FACTUALLY ERRONEOUS

(A) The Wong reference supports the present invention

Much of the Examiner rejection is grounded on the Wong reference. Apparently, the Examiner believes that the Wong reference is significantly inconsistent with the data obtained in the present invention. It is a misreading of the Wong reference. The Wong reference not only does not discredit the data of the present invention, but provides a forceful support to the present invention: measuring the blood level of beta-catenin mRNA is a good tool for detecting colorectal cancer. It is reliable. It is valuable. This is an indisputable fact clear to anyone with ordinary skill in the art in view of the following data disclosed in the Wong reference:



To put the data in the numerical format, the Wong reference disclosed the beta-catenin mRNA range and median for people with carcinoma, people with ademona and normal people, respectively, as following:

Subjects	beta-catenin mRNA (range) (copies)	beta-catenin mRNA (median) (copies)
Carcinoma	1,480-933,100	8,737
Adenoma	541-2,254	1,218
Normal	0-1,366	291

The data are remarkably consistent with what are disclosed in the present invention. Given the facts that the two sets of data were obtained by two independent labs, at different times with different experiment settings, the discrepancies are not unusual. The discrepancies are immaterial to the issue of enablement, which is based on the correlation taught by the present invention. The correlation is corroborated, rather than discredited, by Wong. The specific assay method disclosed in the Wong reference can be viewed as another embodiment of the present invention. The data obtained from the independently designed embodiment undoubtedly and

unambiguously corroborate the operability and value of the claimed invention. It is not uncommon that different embodiments of the same invention may operate differently.

(B) The cited references are misunderstood and misused

(1) *The initial burden is on the Examiner.*

In final office action (page 10 of Final Office Action), the Examiner asserts that the Appellant's previous arguments as being taking "the place of evidence in the record." This characterization is erroneous because the Appellant did not request that those arguments be accepted as evidence of record. They merely represent some commonsense reasoning and augments why the Examiner has misunderstood the disclosure of the references and why these references do not support a *prima facie* case of non-enabling.

It is respectfully pointed out that it is the Examiner's initial burden of showing the application is non-enabling ("[i]f the examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more, the applicant is entitled to grant of the patent." *In re Oetiker*, 24 USPQ 2d 1443, 1444 (Fed. Cir. 1992). The reasoning and augments presented by Appellant (previously and below), via its counsel, go to the issue that the Examiner has not produced a *prima facie* case, and are not presented as evidence to rebut the Examiner's *prima facie* case, which has not been made. In this regard, it is respectfully submitted that no law bars the patent applicant from making arguments based on commonsense and generally accepted scientific principles and practice. For example, the law would not require the statement that "the sun is bigger than the moon" be supported by an affidavit or declaration. The Examiner is free to accept or reject it as being commonsense.

(2) *Diagnosis is enabled by correction, not by absolute level of beta-catenin mRNA*

In a medical measurement, presence or absence of a substance is generally used in a relative sense and the threshold between presence and absence can be predetermined and preset by a person of ordinary skill in the art according to the

specific situation, sensitivity of detection tools and current knowledge of all relevant issues. For example, one with ordinary skill in art, if using measurement settings as disclosed in the Wong reference and obtaining results similar to what Wong obtained, may decide the baseline or threshold to be set at 540, above which the measurement would indicate presence of an abnormal amount of beta-catenin mRNA and need for more invasive check for possible presence of adenoma and carcinoma. It was within the essence of the present invention and within ordinary skill in the art to set the threshold at this level. This is another embodiment and is valuable because most normal people (as the median is 291) would avoid more invasive procedures. Thus, whether beta-catenin mRNA is detectable in most normal persons is not an issue. The issue is whether its level is sufficiently varied among groups of people with different conditions. Both the present invention and the Wong reference unambiguously demonstrated that beta-catenin RNA level is sufficiently different in three different groups of people to have a diagnostic or assessment value, notwithstanding the overlapping measurement ranges among the different groups. Therefore, the fact that beta-catenin mRNA is present in most normal people and the fact the different groups of people have overlapping ranges of beta-catenin mRNA do not support the Examiner's contention that the present invention as claimed is not enabled. The Examiner is free to be unpersuaded by Appellant's forgoing arguments, but it is his or her initial burden to articulate otherwise. For example, to insist that the beta-catenin mRNA being present in normal people would render its blood level measurement non-enabling as a diagnostic means, the Examiner would have to articulate a reason how it would be different from the blood sugar level which is present in normal people, yet it is accepted as a means of indicating diabetes.

(3) The specification needs not disclose the obvious or commonsense

The Examiner seems to require everything be disclosed in the specification (second paragraph, page 13, Final Office Action). However, the law provides that the patent specification "need only be reasonable with respect to the art involved; they need not inform the layman nor disclose what the skilled already possess. They need not describe the conventional ... The intricacies need not be detailed ad absurdum."

General Elec. Co. v. Brenner, 159 USPQ 335, 337 (D.C. Cir. 1968), citing *Loom Co.*

v. Higgins, 105 U.S. (15 Otto) 580 (1882). Also see *Lindemann Maschinenfabrick GmbH v American Host & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984), in which CAFC stated that “[t]he question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is well known in the art.”

(4) The Examiner is creating a straw person argument with an inoperable example by not following the specific teaching of the present specification

Instead of articulating a reason why a person of ordinary skill in art cannot follow the teaching of the present specification to practice the invention, the Examiner attempted to construct an artificial scenario by picking and choosing a part of the present specification and a part of the Wong reference and then mixing them to purposely create something unworkable (see second paragraph, page 11 and entire page 12, Final Office Action). It is incorrect because if two different working machines exemplified as two particular embodiments of an invention, the Examiner cannot argue that the invention is not enabled merely because a nut taken from one machine does not fit well in the other machine and render it operable. It is a straw person argument.

(5) Room for further improvement does not render the invention non-enabling

A patent claim being enabled doesn't mean it would not need further refinement to become more useful or for more applications. While the Wong reference suggested a more intensive study necessary to explore the applicability of the present claimed invention for prognostic use and a large-scale study to decide whether the present invention can be applied to population screening, a patent claim cannot be rejected for lack of enablement simply because someone else mentioned that the claimed subject matter could, with more studies, be extended to further applications. Both prognostic and population screening suggested by Wong are related to further applications of the present invention, not the claimed invention per se.

In fact, the so-called “dominant” patent claims can encompass additional subsequent patents claiming refinements and further applications of the basic idea of the

dominant patent. If following the Examiner's logic, all dominant patents would be invalid for lack of enabling further applications.

(C) The Osmer and Fleischhacker references are irrelevant

It is simply unclear to the Appellant what is the relevance of the Osmer and Fleischhacker references to the enablement issue in the instant case. Neither reference says anything about whether one with ordinary skill in the art is unable to measure the level of the beta-catenin related nucleic acids in the blood using a method taught by the present invention, nor anything about whether one with ordinary skill in the art is unable to appreciate the correlation between the measured level of beta-catenin related nucleic acids and the presence of possible colorectal cancer.

The Osmer reference cannot be viewed as evidence that any single gene is insufficient for a diagnostic method, a proposition that runs contrary to existing gene-based diagnostic methods used in the medical field.

The difference between serum and plasma measurements, taught in the Fleischhacker reference is specific to its own specific settings, says nothing one way or the other, about whether a serum measurement would correlate with a certain disease in other situations. When the plasma measurement correlates with a disease, there is a strong likelihood that a corresponding serum measurement would also similarly correlate. As disclosed in the present invention, it is indeed the case with β -catenin related nucleic acids, both plasma and serum measurements are correlated to the presence of possible colorectal cancer, and the Fleischhacker reference does not say, and cannot say, anything to the contrary about this parallel correlation of the present invention.

CONCLUSION

In view of the foregoing remarks, the Applicant respectfully submits that the rejection under 35 USC section 112, the first paragraph in this case was improper both as a

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matter of law and as a matter of facts. The Board should find the rejected claims allowable. Reversal of the rejection is hereby earnestly solicited.

Respectfully submitted,

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APPENDIX:

EVIDENCE

None

RELATED PROCEEDINGS

None

CLAIMS ON APPEAL

Claim 1: A method for detecting colorectal carcinoma in a patient, comprising:
extracting blood serum or plasma from the patient;
measuring an amount of a nucleic acid associated with encoding catenin in the blood serum or plasma; and
determining a possibility of the presence of colorectal cancer in the patient based on the amount of the nucleic acid measured in the blood serum or plasma.

Claim 2: The method according to claim 1, wherein the catenin is beta-catenin or alpha-catenin.

Claim 3: The method according to claim 1, wherein the nucleic acid is beta-catenin RNA.

Claim 4: The method according to claim 1, wherein the nucleic acid is beta-catenin DNA.

Claim 5 (currently amended): The method according to claim 1, wherein the patient is a human.

Claims 6-29 (canceled).

Claim 30: The method according to claim 3, wherein measuring the amount of beta-catenin RNA is carried out with a RT-PCR method which amplifies a nucleic acid fragment corresponding to a portion of beta-catenin gene.

Claim 31: The method according to claim 30, wherein the RT-PCR method uses a pair of primers identified as SEQ ID NO: 4 and SEQ ID NO: 5.

Claim 32: The method according to claim 30, wherein the RT-PCR method uses a pair of primers identified as SEQ ID NO: 6 and SEQ ID NO: 7.

Claim 33: The method according to claim 30, wherein the RT-PCR method uses a pair of primers identified as SEQ ID NO: 8 and SEQ ID NO: 9.

Claim 34: The method according to claim 4, wherein measuring the amount of beta-catenin DNA is carried out with a PCR method which amplifies a nucleic acid fragment corresponding to a portion of beta-catenin gene.

Claim 35: The method according to claim 34, wherein the PCR method using a pair of primers flanking the 2nd and 3rd introns of beta-catenin gene.

Claim 36: The method according to claim 35, wherein the pair of primers is identified as SEQ ID NO: 10 and SEQ ID NO: 11.

Claim 37: The method according to claim 1, wherein a volume of the blood serum or plasma used is from 2 ml to 5 ml.